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June 22, 1954

Dr. Harris Isbell
U.S. Public Health Service Hospital
Lexington, Kentucky

Dear Dr. Isbell:

I have gotten together all of the information that is presently available on the substance Bufotenine. The source of this is almost entirely confined to a talk given by Dr. Edward Evarts at the American Chemical Society Medicinal Chemistry Symposium at Syracuse which I attended last week.

Monkeys are regularly given doses of 1 or 2 mg/kg of the material I.V. At this level the animals are awake but totally blind for about an hour. Muscle strength seems normal but a profound ataxia prevents walking. The vestibular mechanism doesn't seem to be affected as the animal rights himself if placed down on his back. These treated monkeys are uniformly tractable and will not bite even when fingers are forced into their mouths. They persist in this attitude long after the blindness and ataxia wears off. Monkeys which were given about 6 mg/kg I.V. died in convulsions resembling those produced by strychnine as did some dogs at about 3 mg/kg I.V. The behaviour of dogs at 1 or 2 mg/kg is considerably different from that of the monkeys. Whereas the monkeys lie quietly and are very tractable, the dogs howl and indicate an exceedingly disturbed state of mind.

Dr. Evarts told of the native use of this material. He said that the beans were dried and then powdered and taken as snuff. From the concentration of active principle in the bean, it was calculated that if the nasal cavity of a person were completely stuffed with ground bean, the total dose per man would be about 0.5 mg. Since the natives usually experience a medium to severe intoxication, it would appear that the drug is active in a dose of perhaps 0.1 to 0.5 mg per man.

From all that I can gather, the activity of this material is qualitatively almost identical to that of the drug you have been using but may be quantitatively less potent. I have been told that it is stable and can be given orally, although in Evarts' experiments, the I.V. route was used.

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I hope that I have been able to provide you with enough information here to allow some preliminary trials. The problems of supply and stability, etc., would be vastly simplified if this drug could be used in lieu of the one you have been investigating.

I'm looking forward to seeing you when you are down here next month.

[redacted]

HWB/mk

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LSD DOSE-EFFECT DATA

Mean of Measure	DOSE MCG/KG					
	-0.602 0.25	-0.301 0.5	-0.125 0.75	0 1.0	.176 1.5	0.301 2.0
	NUMBER OF SUBJECTS					
	8	8	8	7	8	6
Respiratory Rate	0.15	0.01	0.43	0.2	0.03	0.15
Body Temperature	-0.48	0.39	0.33	0.21	0.15	0.39
Knee Jerks	1.28**	1.22	1.52	1.71*	1.43	1.52**
Systolic Blood Pressure	1.07	1.11	2.18*	2.56**	2.84*	3.11**
Pupillary Size	0.72	1.88**	3.17**	3.14**	3.87**	3.48**
Number Positive Answers	21	35*	50**	34*	60**	41*
Clinical Grade	0.2	0.75*	1.0**	.71*	1.62**	1.33**

* Significant at 5% level.

** Significant at 1% level.

Notes on LSD Dose-EFFECT Table

1. Data on respiratory rate, body temperature, knee jerks and systolic blood pressure were graphed. The pre-dose values for each measure were averaged and average drawn as base line. Area under curve over 8-hour period past-dose was measured with a planimeter. This yields a figure in square inches ("effect hours") which reflects the total time-action course for the eight-hour period.

2. Average results on 2 placebos for each individual were subtracted from result with various LSD figures, giving a figure reflecting only LSD effect. These figures were then analyzed statistically, using the "t" test for paired observations. The significance ratios are all in terms of that dose against placebo. As yet differences between LSD doses have not been analyzed.

3. Note that respiratory rate & body temperature changes are not significant.

4. Significant changes were obtained in knee-jerks, systolic blood pressure, & pupillary size. The pupillary change is the most sensitive and significant measurement. Although average changes in knee jerks were always in the same direction, changes could not be shown to be significant at all dose levels. This probably was due to the fact that knee jerk was graded clinically, rather than being measured quantitatively.

5. Significant changes were observed in a number of positive answers and in clinical grades at doses of 0.5 mcg/kg and above. Although time has not yet permitted calculation of correlation coefficients, it appears that both these measures will correlate with each other and with blood pressure and pupillary changes. In other words, the degree of pupillary dilatation reflects the degree of mental change and vice versa. Thus, one measure serves as a check on the other.

6. The irregularities in the results at 1.0 and 2.0 mcg/kg are due in part to omission of one very sensitive subject from these dosage levels. This results in a decrease in the mean effect at these doses.

7. Very good dose response curves were obtained (considering the small number of subjects) when mean responses were plotted against log of dose. Variationsfrom straight line were chiefly at those dose levels which did not include the one extremely sensitive individual.